

Please cancel, without prejudice, claims 31 and 38.

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1. **(Thrice Amended)** A method for limiting damage to neuronal cells by ischemic or hypoxic conditions, comprising systemically administering to an individual a *hedgehog* polypeptide in an amount effective for reducing neuronal cell death and necrosis, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

3. **(Thrice Amended)** A method for the treatment of cerebral infarctions which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral infarct volume, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

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4. **(Thrice Amended)** A method for the treatment of cerebral ischemia which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral ischemia, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

5. **(Thrice Amended)** A method for the treatment of stroke which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to treat stroke, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is

encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

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6. **(Thrice Amended)** A method for the treatment of transient ischemia attack which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cell damage caused by a transient ischemic attack, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6.

~~18. **(Reiterated)** The method of claim 5, wherein the stroke is a thrombotic stroke.~~

19. **(Reiterated)** The method of claim 5, wherein the stroke is an embolic stroke.

20. **(Reiterated)** The method of claim 1, wherein the conditions result in cerebral hypoxia.

21. **(Reiterated)** The method of claim 1, wherein the conditions result in progressive loss of neurons due to oxygen deprivation.

22. **(Reiterated)** The method of any of claims 3-6, wherein the patient is treated prophylactically.

23. **(Reiterated)** The method of claim 1, wherein the individual is treated prophylactically.

25. **(Reiterated)** The method of claim 1, wherein the individual is hypotensive.

26. **(Reiterated)** The method of any of claims 1 and 3-6, further comprising administering one or more of an anticoagulant, an antiplatelet agent, a thrombin inhibitor, and/or a thrombolytic agent.

27. **(Reiterated)** The method of any of claims 1 and 3-6, further comprising performing vascular surgery.

28. **(Reiterated)** The method of claim 27, wherein the vascular surgery comprises carotid endarterectomy.

Please enter the following new claims:

39. **(New)** A method for limiting damage to neuronal cells by ischemic or hypoxic conditions, comprising systemically administering to an individual a *hedgehog* polypeptide in an amount effective for reducing neuronal cell death and necrosis, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is at least 80% identical to at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or a bioactive fragment of at least 50 contiguous amino acids thereof.

40. **(New)** A method for the treatment of cerebral infarctions which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral infarct volume, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is at least 80% identical to at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or a bioactive fragment of at least 50 contiguous amino acids thereof.

41. **(New)** A method for the treatment of cerebral ischemia which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral ischemia, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is at least 80% identical to at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or a bioactive fragment of at least 50 contiguous amino acids thereof.

42. (New) A method for the treatment of stroke which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to treat stroke, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is at least 80% identical to at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or a bioactive fragment of at least 50 contiguous amino acids thereof.

43. (New) A method for the treatment of transient ischemia attack which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cell damage caused by a transient ischemic attack, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is at least 80% identical to at least one of SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or a bioactive fragment of at least 50 contiguous amino acids thereof.

44. (New) A method for the treatment of cerebral infarctions which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide and at least one additional agent, in an amount effective to reduce cerebral infarct volume, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, and wherein said additional agent is selected from at least one of an anticoagulant, an antiplatelet agent, a thrombin inhibitor, or a thrombolytic agent.

45. (New) A method for the treatment of cerebral ischemia which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide and at least one additional agent, in an amount effective to reduce cerebral ischemia, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid

sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, and wherein said additional agent is selected from at least one of an anticoagulant, an antiplatelet agent, a thrombin inhibitor, or a thrombolytic agent.

46. (New) A method for the treatment of stroke which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide and at least one additional agent, in an amount effective to treat stroke, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, and wherein said additional agent is selected from at least one of an anticoagulant, an antiplatelet agent, a thrombin inhibitor, or a thrombolytic agent.

47. (New) A method for the treatment of cerebral infarctions which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral infarct volume, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, and wherein said method additionally includes surgery.

48. (New) A method for the treatment of cerebral ischemia which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral ischemia, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, and wherein said method additionally includes surgery.

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49. (New) A method for the treatment of stroke which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to treat stroke, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6, and wherein said method additionally includes surgery.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (Thrice Amended) A method for limiting damage to neuronal cells by ischemic or hypoxic conditions, comprising systemically administering to an individual a *hedgehog* polypeptide in an amount effective for reducing cerebral infarct volume by at least 50% neuronal cell death and necrosis, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 ~~relative to the absence of administration of the *hedgehog* polypeptide.~~

3. (Thrice Amended) A method for the treatment of cerebral infarctions which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral infarct volume by at least 50%, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 ~~relative to the absence of administration of the *hedgehog* polypeptide.~~

4. (Thrice Amended) A method for the treatment of cerebral ischemia which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cerebral ischemia cerebral infarct volume by at least 50%, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 ~~relative to the absence of administration of the *hedgehog* polypeptide.~~

5. (Thrice Amended) A method for the treatment of stroke which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to treat stroke reduce cerebral infarct volume by at least 50%, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 ~~relative to the absence of administration of the *hedgehog* polypeptide.~~

6. (Thrice Amended) A method for the treatment of transient ischemia attack which comprises systemically administering to a patient in need thereof a *hedgehog* polypeptide in an amount effective to reduce cell damage caused by a transient ischemic attack cerebral infarct volume by at least 50%, wherein said *hedgehog* polypeptide comprises an amino acid sequence that (a) binds to a naturally occurring *patched* receptor and promotes *hedgehog* signal transduction, and (b) is encodable by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in at least one of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6 ~~relative to the absence of administration of the *hedgehog* polypeptide.~~